(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 April 2002 (11.04.2002)

PCT

(10) International Publication Number
WO 02/28380 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/US01/31539

(22) International Filing Date: 5 October 2001 (05.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/238,650 6 October 2000 (06.10.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/28380 A2

(54) Title: ORAL DOSAGE FORMS FOR ADMINISTRATION OF THE COMBINATION OF TEGAFUR, URACIL, FOLINIC ACID, AND IRINOTECAN AND METHOD OF USING THE SAME

(57) Abstract: The invention provides a dosage form and a method of administering an anti-tumor composition comprising tegafur, uracil, and folinic acid to potentiate the coadministration of irinotecan.

ORAL DOSAGE FORMS FOR ADMINISTRATION OF THE COMBINATION OF TEGAFUR, URACIL, FOLINIC ACID, AND IRINOTECAN AND METHOD OF USING THE SAME

Related Applications

This application claims the benefit under 35 U.S.C. Section 119(e) of U.S. Provisional Patent Application No. 60/238,650, filed October 6, 2000.

Field Of The Invention

The present invention is directed to an oral dosage form(s) for administration to a warm blooded animal of the combination of tegafur, uracil, and folinic acid to potentionate coadministered irinotecan for the treatment of tumors.

Background Of The Invention

5-Fluorouracil (5-FU) is known anti-tumor agent. The combination of 5-fluorouracil and folinic acid is a known treatment for colorectal cancer. Tegafur (1- (2-tertrahydrofuryl)-5-fluorouracil) is a prodrug of 5-fluorouracil. In vivo, 5-fluorouracil is rapidly inactivated by the enzyme dihydropyridine dehydrogenase (DPD). Uracil competitively inhibits DPD metabolism of 5-FU generated from tegafur. Thus, coadministration of uracil with tegafur results in higher exposures of active 5-FU as compared to tegafur alone. It is known that 5-fluorouracil cannot be administered orally.

U.S. Patent No. 4,328,229 discloses an anti-cancer composition containing 1-(2-tetrahydrofuryl)-5-fluorouracil ("tegafur") and uracil. The composition is used for delivery of 5-fluorouracil to a tumor sensitive to 5-fluorouracil in a warm-blooded animal. It is disclosed that the composition can be administered in a variety of dosage forms including an oral dosage form.

U.S. Patent No. 5,534,513 discloses an anti-tumor composition containing tegafur and uracil in a molar ratio of 1:4. This anti-tumor composition is stated to be further potentiated by the administration of folinic acid or a pharmaceutically acceptable salt thereof. It is disclosed in the '513 patent that the combination can be administered in a variety of dosage forms including an oral dosage form.

Irinotecan ($C_{33}H_{38}N_4O_6$) is a known anti-tumor agent as disclosed in T. Kunimoto et al., Cancer Res., Vol. 47, p. 5944 (1987).

It has been observed that 5-fluorouracil can enhance the activity of irinotecan. However, because 5-fluorouracil cannot be administered orally, the mode of administration for this combination therapy requires a more invasive form of administration such as by intravenous injection, and therefore typically requires administration by trained medical personnel.

It would be an advance in the art of treating tumors, especially colorectal cancerous tumors, if a therapy could be developed employing a

potentiated form of irinotecan through the action of 5-fluorouracil in a convenient dosage form for oral administration.

Summary Of The Invention

The present invention is directed to a dosage form(s) suitable for oral administration to a mammal for the treatment of tumors, especially colorectal tumors, that exhibits a synergistically enhanced effect in combination with irinotecan. In particular, there is provided in accordance with the present invention a dosage form(s) suitable for oral administration to a mammal having a tumor comprising an effective amount of each of tegafur, uracil, and folinic acid or a pharmaceutically acceptable salt thereof to a patient undergoing treatment with irinotecan, wherein said dosage form(s) is a potentiator of irinotecan. In a preferred form of the invention, tegafur and uracil are present in respective amounts sufficient for tegafur to effectively and efficiently convert to 5-fluorouracil. In a particularly preferred form of the invention tegafur and uracil are present in a molar ratio of about 1:4 (*hereinafter referred to as* "UFT").

There is also disclosed a method of orally administering an anti-tumor effective amount of the combination of tegafur and uracil, preferably as UFT, and folinic acid or a pharmaceutically acceptable salt thereof to a mammal having a tumor who is undergoing irinotecan therapy.

The present invention further provides a method for the synergistic treatment of cancer, such as colorectal cancer, which comprises orally administering a synergistically effective amount of tegafur, uracil, and folinic acid or a pharmaceutically acceptable salt thereof, such as calcium folinate, to a mammal undergoing treatment with irinotecan.

Detailed Description Of The Invention

The administration of the combination of tegafur and uracil in amounts sufficient to convert tegafur to 5-fluorouracil (preferably a molar ratio of about 1:4) can be administered orally. It was unexpectedly discovered that oral administration of this combination produced sufficient 5-fluorouracil that potentiation of irinotecan would take place despite the inability of 5-fluorouracil itself to be effectively administered orally. This was surprising because the combination of tegafur and uracil is not totally absorbed in the gut. Thus, it was unexpected that there would be a sufficient blood circulating concentration of 5-fluorouracil available to potentiate irinotecan.

The oral dosage form used in the present invention provides significant advantages over administering the combination by other modes of administration which are more invasive. In the treatment of tumors, a potential reduction in the cost of therapy because skilled medical personnel are not required to administer the drug and the psychological benefits afforded a patient by taking an oral medication provide significant benefits for patient care.

The dosage forms for all oral administration include tablets, powders, granules, and the like. Excipients and additives which may be used include, but are not limited to, lactose, sucrose, sodium chloride, glucose, urea, starch, calcium, kaolin, crystalline cellulose, salicylic acid, methylcellulose, glycerol, sodium alginate, arabic gum and the like. Conventional binders may be used such as glucose solutions, starch solutions, gelatine solutions, and the like. Disintegrators may be used including, but not limited to, dry starch, sodium alginate, agar powder, calcium carbonate, and the like. Absorbents which may be used include, but are not limited to, starch, lactose, kaolin, bentonite, and the like. Lubricants which may be used include, but are not limited to, purified talc, stearic acid salts, boric acid powder, polyethylene glycol and the like.

Tegafur, uracil, and folinic acid preferably provided as the calcium salt "calcium folinate" (leucovorin) are present in the oral dosage form(s) in an amount from about 1 to 70% by weight based on the total weight of the oral dosage form(s). The dosage of each active ingredient for administration on a daily basis is from about 0.1 to 100 mg/kg/day, preferably about 1 to 30 mg/kg/day for tegafur. The preferred dosage for uracil is from about 1 to 50 mg/kg/day. For UFT, i.e. the 1:4 combination of tegafur and uracil, the dosage is from about 200 to 500 mg/m^2/day based on tegafur, preferably from about 250 to 300 mg/m^2/day based on tegafur. Folinic acid or a pharmaceutically acceptable salt thereof may be administered in an amount

from about 0.1 to 500 mg/kg/day, but preferably is administered as calcium folinate in a fixed dose of about 90 mg/day. The oral dosage form(s) may be administered in a single dose(s) or in divided doses typically up to 3 times a day. Irinotecan is typically administered in a non-oral mode of administration, typically intravenously. Based on body surface area, the dosage may range from about 100 to 400 mg/m^2/day, preferably from about 200 to 300 mg/m^2/day.

Those of ordinary skill in the art would have the knowledge to adjust the above stated dosage ranges for UFT, folinic acid or a pharmaceutically acceptable salt thereof, and irinotecan as needed based on body surface area and/or in the event of toxicity. In accordance with the present invention, the combination of tegafur and uracil (e.g. UFT) results in a sufficient amount of 5-fluorouracil available to potentiate irinotecan to improve the availability and potency of irinotecan in the treatment of tumors, especially colorectal tumors.

The following examples are exemplary of the claimed invention, but are not intended to limit the invention as encompassed by the full disclosure of the invention set forth herein.

EXAMPLE 1

This study assessed the *in vivo* maximum tolerated dose (MTD), the side effect profile and the dose limited toxicity (DLT) of irinotecan combined with UFT (tegafur and uracil in a molar ratio of 1:4) plus calcium folinate (leucovorin).

An open label, phase I/II trial with escalating doses of UFT and irinotecan was conducted with a fixed dose of calcium folinate at 90 mg/day. Up to five cohorts of three to six patients comprised the test patient study. Entry criteria for the study included, but was not limited to, a histological or cytological confirmed metastatic colorectal carcinoma, no concurrent radiotherapy, no prior chemotherapy for metastatic disease, ECOG performance status of 0-2, no brain metastatic disease, and adequate hematological, renal and hepatic function.

The dosages for UFT, calcium folinate and irinotecan for each level are escalated as shown below in Table 1.

Table 1

Cohort No.	Dose Level	UFT Dosage (mg/m^2/day)	Calcium Folinate Dosage (mg/day)	Irinotecan Dosage (mg/m^2/day)
1	0	250	90	200
2	1	250	90	250
3	2	250	90	300
4	3	300	90	300
5	4	300	90	300

The treatments were given on a three-week cycle until progressive disease or unacceptable toxicity occurred. UFT and calcium folinate were given orally on days 1-14 of each cycle; irinotecan was administered intravenously on day 1 (d1) of each cycle.

Six patients were entered at each dose level. After all patients had safely completed one cycle of treatment, the dose was escalated. The study continued to each progressive level until the maximum tolerated dose (MTD) was experienced. The MTD was defined as the dose level at which greater than 1/3 or 2/6 of the patients experienced a dose limiting toxicity (DLT) during the first cycle of treatment.

The cohort below the MTD was then expanded to 20 patients. The DLT was defined as follows:

a. Grade 3/4 neutropenia complicated by fever greater than 38°C., I.V. antibiotics or grade 3/4 diarrhea, or

b. Grade 4 thrombocytopenia prolonged or complicated by bleeding or requiring platelet transfusion, or

c. Grade 3/4 neutropenia or thrombocytompenia for more than 7 days, or

d. Grade 3/4 non-hematological toxicity with the exception of alopecia, nausea and vomiting, or

e. Grade greater than or equal to 2 renal, hepatic, cardiac or pulmonary toxicity or

f. A treatment delay of greater than two weeks prior to the start of the next cycle of treatment.

Patients qualified for the test protocol if they met the following criteria:

- Histological or cytological confirmed advanced/metastatic colorectal carcinoma
- Measurable disease (1 cm in at least one dimension)
- Age >18 years
- Either no prior chemotherapy or adjuvant chemotherapy for advanced or metastatic disease (>6 months prior to study entry) suitable for fluoropyrimidine or topoisomerase I inhibitor treatment
- ECOG performance status 0-2, life expectancy >3 months
- Serum creatinine 1.5 x UNL

  Serum bilirubin 1.5 x UNL
- Written informed consent

Patients were disqualified for the test protocol if they had bowel obstruction, any condition which would affect UFT and/or calcium folinate absorption, or prior radiotherapy unless palliative or for adjuvant therapy of rectal carcinoma.

The test patients were evaluated in the following manner:

- Patients receiving at least one cycle of treatment were evaluated for toxicity.
- Patients receiving at least 2 cycles of treatment or who developed rapid tumor progression or who died of progressive disease were evaluated for response. Also patients who discontinued treatment, or who died, due to a treatment related toxicity prior to response evaluation were considered evaluated for response.
- Disease was assessed every 3 cycles and the response evaluated according to WHO criteria (Miller et al., 1981)

The study was closed after a total of 33 patients were registered for the study. Six patients were enrolled in each of Cohort Nos.1, 2, and 3. An additional patient was registered to Cohort No. 1, but was removed from the study before receiving treatment.

MTD was achieved at Cohort No. 3 (250 mg/m^2/day UFT and 300 mg/m^2/day 1 irinotecan). Accordingly, Cohort No. 2 was expanded to 20

patients. The pretreatment characteristics of the patients assigned to each cohort is shown in Table 2.

Table 2

Pre-treatment Characteristics				
	Cohort 1 n=7	Cohort 2 n=20	Cohort 3 n=6	Total n=33 (%)
Gender				
Male	3	11	4	18 (55)
Female	4	9	2	15 (45)
Performances Status				
0	2	5	2	9 (27)
1	5	12	3	20 (61)
2	0	2	1	3 (9)
3	0	1*	0	1 (3)
Age				
Median	62	65	68	63
Range	35-74	47-80	19-63	19-80
Primary Site				
Colon	4	7	5	16 (48)
Rectum	3	9	1	13 (39)
Colorectal	0	4	0	4 (12)

*Not due to malignancy

The median number of cycles was 6. (range 1-11)

The treatment was generally well tolerated. The most common grade 3/4 toxicities were nausea, asthenia, diarrhea and neutropenia. The toxicity profile of the patients is shown in Table 3.

Table 3

CTC Worst grade 3/4 Adverse Events				
	Cohort 1 n=6	Cohort 2 n=20	Cohort 3 n=6	Total n=32
Digestive system				
Nausea	2	3	2	7
Vomiting	0	2	1	3
Diarrhea	0	3	3	6
Anorexia	0	1	1	2
Intestinal Obstruction	0	1	1	2
Constipation	1	0	0	1
Dyspepsia	1	0	0	1
Other non-hematologic				
Asthenia	1	6	2	9
Headache	1	0	0	1
Pain	1	1	2	4
Myocardial Infarction	0	1	0	1
Infection	0	1	0	1
Respiratory system	0	1	1	2
Dyspnea	0	1	1	2
Somnolence	0	1	0	1
Epistaxis	0	0	1	1
Hematologic				
Neutropenia	0	8	2	10
Febrile Neutropenia	0	3	1	4

Dose limiting toxicities (DLT) were experienced by patients in Cohort Nos. 2 and 3 and included diarrhea and neutropenia as shown in Table 4.

Table 4 - DLT (Experienced in first cycle treatment)

Cohort 2 (250 mg/m^2/d UFT and 250 mg/m^2/d1 irinotecan)	**Cohort 3** (250 mg/m^2/d UFT and 300 mg/m^2/d1 irinotecan)
Grade 4 diarrhea	Grade 3 diarrhea
	Grade 3 febrile neutropenia
	Grade 4 febrile neutropenia

The response of the patients of Cohort Nos. 1-3 to treatment is shown in Table 5.

Table 5

	Cohort 1	Cohort 2	Cohort 3	Total (%)
EVALUATED				
Complete response (CR)	0	0	1	1
Partial response (PR)	0	5	1	6
Stable disease	2	6	0	8
Progressive disease	0	1	1	2
Response rate (CR and PR)		35.7%		33.3%
Indeterminable	0	2	2	4
Total	2	14	5	21

Of the 21 patients currently undergoing assessment the response to treatment was assessed according to criteria established by the World Health

Organization ("WHO") as described in Miller, A.B. et al., Cancer 11 (1981). A complete response in which the disappearance of all tumor lesions is confirmed by two independent observations at least four weeks apart, has been observed in one patient (4.8%). A partial response, in which there is generally a decrease of at least 50% in the size of tumor lesions was observed in 6 patients (28.6%). A stable disease situation was observed in 8 patients (38.1%) where there was no change in the disease (i.e. a decrease in tumor size of less than 50% or an increase in tumor size of less than 25%) confirmed by two independent observations at least 4 weeks apart. A progressive disease situation was observed in 2 patients (9.5%). This category includes the appearance of any new, previously unidentified lesions or occurrence of malignant pleural effusion or ascites and/or an increase by at least 25% in the size of one or more measurable lesions.

Four patients exhibited early toxicity and were not therefore evaluated while one patient did not receive treatment. Eleven patients have not yet been assessed. Thus, the overall response rate for the study was 33.3% with a response rate of 35.7% at the dosage given to Cohort No. 2.

Based on the results shown in Table 5, the combination of UFT, calcium folinate (leucovorin) and irinotecan is well tolerated and shows anti-tumor activity.

What Is Claimed Is:

1. A method of administering an anti-tumor effective amount of the combination of tegafur, uracil, and folinic acid or a pharmaceutically acceptable salt thereof, to a mammal undergoing treatment with irinotecan comprising administering to the mammal having a tumor said combination in oral dosage form(s).

2. The method of claim 1 wherein the amount of tegafur and uracil is sufficient to produce an effective amount of 5-fluorouracil sufficient to potentiate the activity of irinotecan.

3. The method of claim 1 wherein tegafur and uracil are present in a molar ratio of about 1:4, respectively.

4. A dosage form suitable for administration to a mammal having a tumor and undergoing treatment with irinotecan comprising an effective amount of each of tegafur, uracil, and folinic acid or a pharmaceutically acceptable salt thereof in oral dosage form.

5. The dosage form of claim 4 wherein the amount of tegafur and uracil is sufficient to produce an effective amount of 5-fluorouracil sufficient to potentiate the activity of irinotecan.

6. The dosage of claim 5 wherein tegafur and uracil are present in a molar ratio of about 1:4 sufficient to potentiate the activity of irinotecan.

7. A method for the synergistic treatment of cancer which comprises orally administering a synergistically effective amount of tegafur, uracil, and folinic acid or a pharmaceutically acceptable salt thereof to a mammal undergoing treatment with irinotecan.

8. The method according to claim 7 wherein the cancer is colorectal cancer.

9. The method according to claim 7 wherein tegafur and uracil are present in a molar ratio of about 1:4, respectively.

10. The method according to claim 7 wherein tegafur is orally administered at a dosage of about 1 to 30 mg/kg/day, uracil is orally administered at a dosage of about 1 to 50 mg/kg/day, and calcium folinate is orally administered at a fixed dosage of about 90 mg/day.

11. The method according to claim 7 wherein the mammal is treated with irinotecan at a dosage of about 100 to 400 mg/m^2/day.

12. The method according to claim 7 wherein the mammal is treated with irinotecan at a dosage of about 200 to 300 mg/m^2/day.

13. A method for the synergistic treatment of cancer which comprises orally administering a synergistically effective amount of UFT and folinic acid or a pharmaceutically acceptable salt thereof to a mammal undergoing treatment with irinotecan.

14. The method according to claim 13 wherein the cancer is colorectal cancer.

15. The method according to claim 13 wherein UFT is orally administered at a dosage of about 200 to 500 mg/m^2/day based on tegafur, calcium folinate is orally administered at a fixed dosage of about 90 mg/day, and the mammal is treated with irinotecan at a dosage of about 100 to 400 mg/m^2/day.

16. The method according to claim 13 wherein UFT is orally administered at a dosage of about 250 to 300 mg/m^2/day based on tegafur, calcium folinate is orally administered at a fixed dosage of about 90 mg/day, and the mammal is treated with irinotecan at a dosage of about 200 to 300 mg/m^2/day.

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(43) International Publication Date
11 April 2002 (11.04.2002)

PCT

(10) International Publication Number
WO 02/028380 A3

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Published:
— *with international search report*

(88) Date of publication of the international search report:
3 April 2003

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WO 02/028380 A3

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INTERNATIONAL SEARCH REPORT

In nal Application No
PCT/US 01/31539

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P35/00 A61K31/513 A61K31/505 A61K31/4745

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
MEDLINE, EMBASE, BIOSIS, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TWELVES C: "UFT plus calcium folinate/ irinotecan in colorectal cancer." ONCOLOGY, (1999 JUL) 13 (7 SUPPL 3) 51-4. , XP008010476 the whole document ---	1-16
X	ARTRU P. ET AL: "'Update on new treatments for cancer!. LE POINT SUR DE NOUVEAUX TRAITEMENTS EN CANCEROLOGIE." PRESSE MEDICALE, (8 APR 2000) 29/13 (704-705). , XP008010477 page 704, column 3, paragraph 1 -----	1-16

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 December 2002	09/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

national application No.
PCT/US 01/31539

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-3 and 7-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.